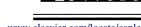


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[¹³¹I]MIBG and topotecan: A rationale for combination therapy for neuroblastoma

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Abstract

MIBG is selectively concentrated in neuroblastoma cells, and radioiodinated MIBG has been used with some success for targeted radiotherapy. However, long-term cure remains elusive, and the topoisomerase I inhibitor topotecan may improve upon existing [¹³¹I]MIBG therapy.

While synergistic killing by combinations of ionising radiation and topoisomerase I inhibitors has been reported, there is no consensus on optimal scheduling. Furthermore, there has been no attempt to demonstrate radiopotentiation by topoisomerase I inhibitors and targeted radiotherapy. We are investigating various scheduled combinations of topotecan and [131]MIBG on neuroblastoma cells, and preliminary data suggests that topotecan induces increased accumulation of [131]MIBG in vitro. © 2005 Elsevier Ireland Ltd. All rights reserved.

Keywords: [131]MIBG; Topotecan; Targeted radiotherapy

1. Targeted radiotherapy for neuroblastoma

Neuroblastoma, the most common extracranial solid tumour of childhood, has a long-term survival rate of only 15% [1]. It is a heterogeneous disease and, at presentation, 67% of neuroblastoma patients have metastases [2]. While patients with stages 1 and 2 disease can usually be treated surgically, without the need for radiotherapy and/or chemotherapy [2], patients with inoperable stages 3 and 4 (with the exception of patients with stage 4S, who generally display spontaneous regression without intensive intervention [2,3]), require intensive treatments, or 'megatherapies', involving combinations of highdose myeloablative chemotherapy with total body irradiation (TBI) and stem cell rescue [1,2]. However, despite the use of such aggressive therapies, in recent years there has been no substantial improvement in the survival rates of patients with advanced disease [4].

It has previously been established that neuroblastoma tumours are radiosensitive [5-7], and external beam irradiation has been used extensively in

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the treatment of both localised and metastatic neuroblastoma tumours [8]. However, the maximum deliverable dose of whole body irradiation is limited by the intolerance of normal tissue.

This problem can be overcome by targeted radiotherapy, where cytotoxic radionuclides are conjugated to tumour-seeking agents, leading to the selective irradiation of malignant foci, with the sparing of normal tissues [9]. The use of tumour targeting radiolabelled agents promises high tumour specificity and improved penetration without evoking an immune response [10]. Furthermore, while heterogeneous uptake of the radioactive agent can result only in a fraction of tumour cells being successfully targeted, energy released by decay of the radioisotope emanates from the targeted portion of the tumour in three dimensions, causing damage to neighbouring cells that have not accumulated the radiolabelled drug [11]. Therefore, even if the success rate of transfer of the radiolabelled agent to tumour cells is less than 100%, underdosing of the tumour is circumvented. Because neuroblastoma is a radiosensitive tumour, it is suitable for targeted radiotherapy, using [131]MIBG.

Meta-iodobenzylguanidine (MIBG), a derivative of the adrenergic neurone-blocking drugs bretylium and guanethidine, is a structural analogue of noradrenaline. 85-90% of neuroblastoma cells express the noradrenaline transporter (NAT), a 12-spanning integral membrane protein responsible for the active intracellular accumulation of catecholamine neurotransmitters [12,13]. MIBG is also selectively concentrated in neuroadrenergic tissue and NATexpressing tumours by this process [12,13], and tracer doses of radioiodinated MIBG have been used successfully for diagnostic scintigraphy of tumours derived from the neural crest [14]. It is expected that the ability of neural crest-derived tumours to accumulate and retain high concentrations of [131]MIBG will lead to a therapeutic use for this drug [8].

Targeted therapy using [¹³¹I] MIBG has induced favourable remissions in some patients when used as a single agent [15–17]. However, long-term cure remains elusive, and the full potential of this therapy may only be realised when it is combined with other agents [18]. One such agent with the potential to improve [¹³¹I]MIBG therapy is the topoisomerase I inhibitor topotecan (TPT).

2. Topoisomerase I

Topoisomerase I (Topo I) is a nuclear enzyme that relaxes supercoiled DNA and plays a crucial role in DNA replication and in transcription [19–21]. Topo I removes the topological tension in front of replication forks by inserting a nick on one of the DNA strands and allowing the other strand to pass through the cleavage site, before re-sealing the nick. During this process, an intermediate state is formed by transient covalent bonding between the tyrosine residues of the Topo I and the 3' termini of the nicked strand (the so-called 'cleavable complex') [20,21].

3. Inhibitors of topoisomerase I: camptothecin and topotecan

Camptothecin (CPT), an alkaloid extract of the tree *Camptotheca acuminata*, was first identified in 1966 as exhibiting antitumour activity in murine leukemia models [20], although it was not until 1988 that the mode of action was identified as Topo I inhibition [22]. The hypothesised cytotoxic mechanism of camptothecin is known as the fork collision model. Briefly, CPT binds to, and stabilises the normally transient cleavable complex, inhibiting the Topo I-induced religation step. During the next round of DNA replication, collision of the stabilised Topo I-DNA complex with the replication fork results in an irreversible double strand break, leading to cell cycle arrest and cell death [20,23].

Clinical trials of CPT were carried out in 1970s. However, these were terminated due to excessive and unpredictable toxicity [20,23]. Instead, researchers attempted to synthesise derivatives of camptothecin which would exhibit lower toxicity and greater solubility in water. This led to the identification of a new class of campotothecin analogues, including the semi-synthetic derivative topotecan.

Topotecan has been entered into clinical trials for neuroblastoma, and has shown effectiveness as a single agent in phase I/II trials [24–26]. Furthermore, when combined with other chemotherapeutic agents (for example, topotecan given in combination with cyclophosphamide in phase II trials [27], and topotecan given in combination with myeloablative doses of thiotepa and carboplatin [28]), encouraging

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